

## Validation of the ‘Test of the Adherence to Inhalers’ (TAI) for Asthma and COPD Patients

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### Abstract

**Background:** To validate the ‘Test of Adherence to Inhalers’ (TAI), a 12-item questionnaire designed to assess the adherence to inhalers in patients with COPD or asthma.

**Methods:** A total of 1009 patients with asthma or COPD participated in a cross-sectional multicenter study. Patients with electronic adherence  $\geq 80\%$  were defined as adherents. Construct validity, internal validity, and criterion validity were evaluated. Self-reported adherence was compared with the Morisky-Green questionnaire.

**Results:** Factor analysis study demonstrated two factors, factor 1 was coincident with TAI patient domain (items 1 to 10) and factor 2 with TAI health-care professional domain (items 11 and 12). The Cronbach’s alpha was 0.860 and the test-retest reliability 0.883. TAI scores correlated with electronic adherence ( $\rho=0.293$ ,  $p=0.01$ ). According to the best cut-off for 10 items (score 50, area under the ROC curve 0.7), 569 (62.5%) patients were classified as non-adherents. The non-adherence behavior pattern was: erratic 527 (57.9%), deliberate 375 (41.2%), and unwitting 242 (26.6%) patients. As compared to Morisky-Green test, TAI showed better psychometric properties.

**Conclusions:** The TAI is a reliable and homogeneous questionnaire to identify easily non-adherence and to classify from a clinical perspective the barriers related to the use of inhalers in asthma and COPD.

**Key words (MeSH terms):** anti-asthmatic agents, administration and dosage; inhalers; medication adherence; medication non-adherence; questionnaires; pulmonary disease, chronic obstructive, drug therapy; validation studies

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## Introduction

IT HAS BEEN ESTIMATED that the degree of compliance with inhaled drug therapy in patients with asthma and chronic obstructive pulmonary disease (COPD) does not surpass 50%.<sup>(1,2)</sup> In these patients, non-adherence or inhaler mishandling increases mortality, morbidity, and health care resource utilization.<sup>(3–6)</sup> Factors related to adherence with inhaled therapy include complexity of the inhalation regimen, peculiarities of inhaler devices, type of inhaled agent, and a variety of patient beliefs and sociocultural and psychological factors.<sup>(7)</sup> Therefore, promoting optimal medication adherence is essential to optimize the benefits of treatment. Consequently, measurement of the degree of adherence to inhaled treatment in each individual patient becomes increasingly important in daily practice.

Adherence to medication is mainly assessed by direct anamnesis with the patient, which invariably underestimates the incidence of non-adherence rates. Although standardized patient self-completed questionnaires for measuring medication adherence have been developed,<sup>(8–10)</sup> its real use in clinical practice is scarce. Moreover, some features make them inappropriate because they are not adequately validated, not specific for inhaler devices,<sup>(8–10)</sup> or only applicable to certain patient populations (asthmatics) or particular inhaled agents (corticosteroids).<sup>(10)</sup>

A further limitation of these questionnaires is a doubtful clinical usefulness to identify barriers to medication adherence and patients at risk of non-adherence. Non-adherent behavior has been broadly classified as erratic, deliberate, and unwitting non-adherence.<sup>(11,12)</sup> Up to the present time, however, these typologies have not been reflected in any particular instrument to assess adherence to inhaled therapy. Knowledge of behavior patterns of non-adherence and, particularly, barriers to treatment adherence is clinically relevant to deliver tailored patient education strategies.

With the objective to provide a new questionnaire specifically designed to establish self-reported adherence to inhaler devices and to help clinicians to assess non-adherence barriers related to inhaled therapy in adult asthma and COPD patients, we developed the Test of Adherence to Inhalers (TAI). Initially, a multidisciplinary panel of health care professionals involved in respiratory diseases built, in a pilot study, a test draft version with 12-items. The aim of this study was to validate and to evaluate the psychometric properties of the proposed 12-item TAI.

## Materials and Methods

### *Development, domains, items, and scores of the TAI*

The TAI was developed in Spanish and was built in three phases. First, the items that made the first version of the questionnaire were derived from a review of the literature<sup>(8,11,13)</sup> and suggestions of the study scientific committee, which lead to a preliminary version that was tested in a group of 10 patients with asthma and/or COPD patients in order to check the intelligibility of the questionnaire. In the second phase, a multidisciplinary panel of 192 investigators composed by pulmonologists, allergists, primary care physicians, and specialized nurses worked together in order to reach a consensus on the items to be included in the questionnaire (based on the Delphi method).<sup>(14)</sup> In the third phase, a pilot study was

performed with the aim to produce a final version (beta version) of the TAI, prior to the validation study.

The final version of the questionnaire included 12 items (Table 1) with two main domains, the patient (items #1 to #10) and the health professional (items #11 and #12) domain. In fact, the TAI consists of two complementary questionnaires: the 10-items TAI was designed to identify non-adherent patients and to establish the non-adherence level, whereas the 12-items TAI was designed to guide clinically the non-adherence patterns.

In the 10-items TAI, each item scored from 1 to 5 (where 1 was the worst possible score and 5 was the best possible score), with a range from 10 to 50. The 12-items TAI, also includes items #11 and #12 of the health care professional and scored as 1 or 2 (where 1 was bad and 2 was good), with a range from 2 to 4. The latter items were designed to identify two possible causes of unwitting non-adherent behavior. An erratic and deliberate non-adherent behavioral pattern was defined in the presence of scores  $\leq 24$  for items #1 to #5 and items #6 to #10, respectively. The unwitting pattern was defined in the presence of a score 1 in at least one of the #11 or #12 items of the questionnaire.

In the pilot study, the questionnaire was fulfilled by 50 patients (29 patients with asthma and 21 with COPD), showing a kappa index of 0.858 between independent observers for items #11 and #12.

### *Study design and participants*

Between March 2013 and March 2014, a cross-sectional multicenter study was conducted to validate the TAI instrument. Eligible patients were Spanish speaking men and women, over 18 years of age, treated with inhaled medications for at least 6 months before enrolment. Subjects were consecutively enrolled from the outpatient visits of the participant centers. Patients with inability to fulfill the questionnaire and/or to use inhaler devices were excluded. Asthma and COPD were defined according to the respective current international guidelines.<sup>(15,16)</sup> A total of 194 investigators from 139 pulmonology, allergology, and primary care centers participated in the study.

The control group (electronic adherence group) was made up of smartphone user patients with asthma using electronic inhaler devices (Smart-inhalers) (Nexus6 Ltd., Auckland, New Zealand), which silently recorded the date and time of each actuation.<sup>(17)</sup> These patients were participating in an ongoing study aimed to assess asthma control using electronic medication monitoring, and also were consecutively enrolled from the outpatient visits of the same participating centers. For the purpose of the present study, the inhaler device used (pressurized metered dose inhaler, pMDI, Turbohaler® or Diskus®) was connected to a specific smart-inhaler.

The study was approved by the Clinical Research Ethics Committee (registration number 2013/8650) of the Hospital Clinic of Barcelona (Spain). Written informed consent was obtained from all participants.

### *Study procedures*

A flow-chart of the study procedures is shown in Figure 1. All study participants attended two consecutive clinical visits 15 days apart. At visit 1, written informed consent was obtained and data on demographics, sociocultural level, and asthma or COPD history were recorded. Also, all patients completed a validated Spanish version of the Morisky-Green

TABLE 1. DESCRIPTION OF TEST OF THE ADHERENCE TO INHALERS (TAI) QUESTIONNAIRE

| <i>Patient domain: questions, responses (scores)</i>                                                           |                    |                          |                               |           | Score  |
|----------------------------------------------------------------------------------------------------------------|--------------------|--------------------------|-------------------------------|-----------|--------|
| 1. During the last 7 days, how many times did you forget to take your usual inhalers?                          |                    |                          |                               |           |        |
| All (1)                                                                                                        | More than half (2) | Approximately a half (3) | Less than half (4)            | None (5)  | 1 to 5 |
| 2. Do you forget to take inhalers?                                                                             |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 3. When you feel good about your illness, do you stop taking your inhalers?                                    |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 4. When you are on vacation or weekend, do you stop taking your inhalers?                                      |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 5. When you are nervous or sad, do you stop taking your inhalers?                                              |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 6. Do you stop taking your inhalers because of fear of side effects?                                           |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 7. Do you stop taking your inhalers because of considering they are useless to treat your condition?           |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 8. Do you take fewer inhalations than those prescribed by your doctor?                                         |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 9. Do you stop taking your inhalers because you believe they interfere with your everyday or working life?     |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| 10. Do you stop taking your inhalers because you have difficulties to pay them?                                |                    |                          |                               |           |        |
| Always (1)                                                                                                     | Mostly (2)         | Sometimes (3)            | Rarely (4)                    | Never (5) | 1 to 5 |
| <i>Health care professional domain: questions, responses (scores)</i>                                          |                    |                          |                               |           |        |
| 11. Does the patient remember the prescribed regimen (dose and frequency)? (checking the medical record)       |                    |                          |                               |           |        |
| No (1)                                                                                                         |                    |                          | Yes (2)                       |           | 1 or 2 |
| 12. The technique of using the evaluated inhaler device by the patient is* (checking the inhalation technique) |                    |                          |                               |           |        |
| With critical mistakes (1)                                                                                     |                    |                          | Without critical mistakes (2) |           | 1 or 2 |

\*Critical mistakes: 1. Pressure metered dose inhalers (pMDIs): do not remove the cover, do not hold the inhaler in a vertical position, firing the device before beginning inspiration, inhalation stopped, inhalation too fast, incorrect insertion of MDI into the inhaler camera, several device firing in the same inhalation, no breath hold after inhalation, cough during inhalation. 2. Dry power inhalers (DPIs): do not open the inhaler, do not prime properly, place the device down after preparation of the dose (before inhalation), blow into the device before inhalation, inhalation not deeply and forcefully, no breath hold after inhalation.

test,<sup>(8,9)</sup> and the TAI questionnaire administered. Information related to the feasibility of the TAI was also collected, such as the time needed to complete the questionnaire and if complementary explanations to understand the questions of the items were required.

Clinical asthma control was assessed with the Asthma Control Test (ACT)<sup>(18,19)</sup> (an ACT score  $\geq 20$  identified well-controlled asthma patients), and COPD clinical status was evaluated with the COPD Assessment Test (CAT)<sup>(20)</sup> (CAT  $\leq 10$  identified mild COPD patients). Spirometry was performed according to the European Respiratory Society/American Thoracic Society guidelines<sup>(21)</sup> using the predicted values for Mediterranean population.<sup>(22)</sup> At visit 2, the Morisky-Green test and TAI were also administered.

Patients in the electronic adherence group also completed the Morisky-Green test and the TAI questionnaire. In these patients, the main measure of electronic adherence was the percentage of inhalations performed correctly between visits 1 and 2. Patients were defined as adherents when  $\geq 80\%$  of the doses prescribed were taken, intermediate adherent when took between 50% and 80%, and non-adherent when took  $\leq 50\%$ .<sup>(10,23)</sup> To correct the bias related to a possible error in handling of the electronic inhaler being a new device, the first two actuations recorded were not included in the analysis.

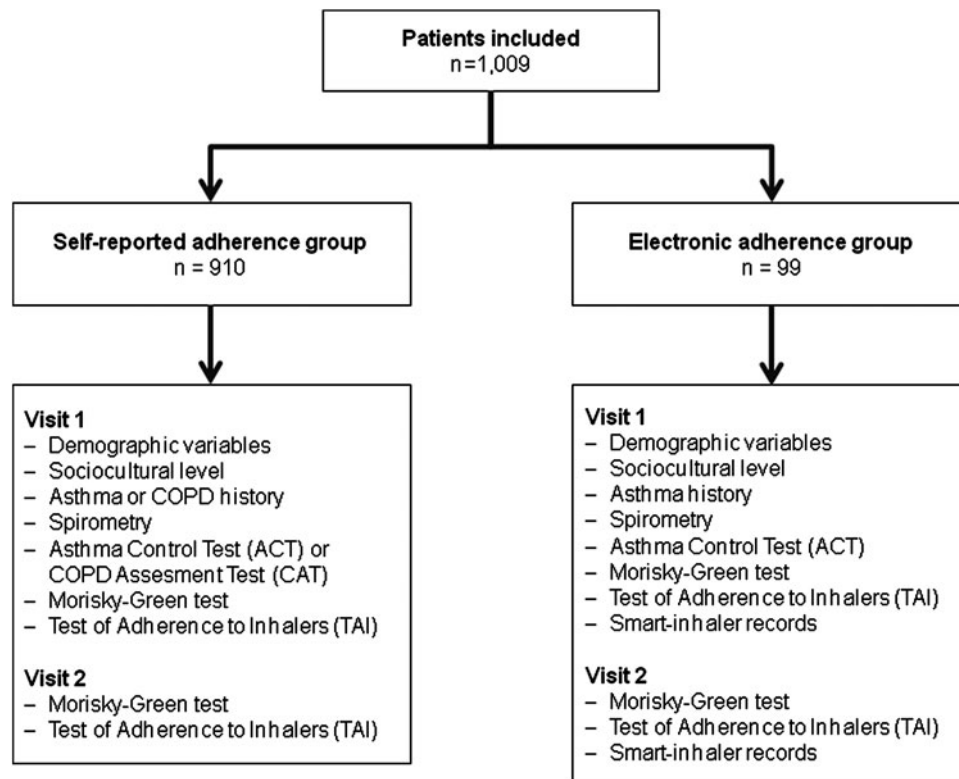
Adherence rates were capped at 100% to avoid dump doses or unintentional actuation.<sup>(13)</sup>

#### Sample size calculation and statistical analysis

The sample size was calculated to detect small differences in the TAI scores between visits 1 and 2. Thus, accepting a significance level of 5% and a power of 80%, 870 patients were required to detect differences  $\geq 0.2$  standard deviations in scores between the two administrations of the questionnaire. A 10% percentage of patients lost to follow-up or with incomplete data were established.

Categorical variables are expressed as absolute and relative frequencies and percentages, and quantitative variables as mean and standard deviation (SD) or median and range (minimum, maximum). To assess the construct validity of the technique of principal component factor analysis with Varimax rotation was used to identify chasing one-dimensional or multidimensional structure of the questionnaire. The appropriateness of factor analysis was verified by measurement of Kaiser-Meyer-Olkin (KMO)<sup>(24,25)</sup> and Bartlett's test of sphericity.<sup>(26)</sup> Internal reliability was measured with the Cronbach's alpha coefficient.<sup>(27)</sup>

The test-retest reliability of the questionnaire was analyzed using the intraclass correlation coefficient (ICC).<sup>(28)</sup> The



**FIG. 1.** Flow-chart of the study design and procedures.

criterion validity was made by comparing the percentage of electronic adherence with self-adherence reported in the TAI score. Sensitivity, specificity, positive and negative predictive values were calculated. Cut-offs of the most favorable balance between sensitivity and specificity with the corresponding received operating characteristics (ROC) curves and the area under the curve (AUC) were determined. The Mann-Whitney *U* test was used for the comparison of quantitative variables and the chi-square ( $\chi^2$ ) test for categorical variables. Correlation between two measures was assessed with the Spearman's rank-order correlation coefficient ( $\rho$ ). Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) (version 17.0 for Windows). Statistical significance was set at  $p < 0.05$ .

## Results

### *Characteristics of the study population*

A total of 910 patients were included in the self-reported adherence group (500 asthma and 410 COPD) and 99 asthma patients in the electronic adherence group. Socio-demographic data, clinical features and results of pulmonary function tests are shown in Table 2. Patients in both groups were not comparable given that patients in the electronic adherence group were asthmatics, with a higher proportion of women, younger age, better education level and lung function. However, patients with asthma in the self-reported and electronic adherence groups were similar except for a higher percentage of never smokers (70.8% vs. 58.6%,  $p=0.016$ ) and patients who received previous inhaler education (79.5% vs. 63.9%,  $p=0.001$ ) in the self-reported

adherence group. Differences according to age strata or education level were not found.

### *Psychometric properties of TAI*

Scores of the two domains (patient and health care professional) of the TAI are shown in Table 3. The electronic adherence group scores were significantly higher than the self-reported adherence group in the patient domain.

Sampling adequacy for factor analysis assessed with the KMO and the Bartlett's test was appropriate, with a coefficient of 0.905. Factor analysis showed a probable structure of two factors, which explained 51% of the total variance of results. The first factor included items #1 to #10, which was consistent with the patient domain, and the second factor included items #11 and #12 in agreement with the health care professional domain (see Supplementary Table S1; supplementary material is available online at [www.liebertpub.com/jamp](http://www.liebertpub.com/jamp)).

Internal reliability of TAI showed a good inter-item correlation with a Cronbach's alpha coefficient of 0.873 for the 10-items patient domain. The test-retest reliability showed an ICC of 0.883. The mean time needed to fulfill the questionnaire was 6 (5.3) minutes. A total of 151 (15%) patients required supplementary clarifications to complete the patient domain.

In the electronic adherence group, 46 (46.5%) patients were classified as adherents and the remaining 53 (53.5%) as non-adherents. Adherent patients as compared with non-adherent patients showed slightly higher scores in the 10-items patient domain score (48.5 [3.0] vs. 46.8 [4.0]). These differences were statistically significant ( $p=0.02$ ). In relation to the criterion validity, TAI scores correlated with electronic adherence for the 10-items TAI scores ( $\rho=0.286$ ,  $P=0.01$ ).

TABLE 2. SOCIODEMOGRAPHIC, CLINICAL CHARACTERISTICS, AND SPIROMETRIC DATA

| Data                                              | Self-reported adherence group (n=910) |                |                 | Electronic adherence group (n=99) | P value* |
|---------------------------------------------------|---------------------------------------|----------------|-----------------|-----------------------------------|----------|
|                                                   | All patients                          | COPD (n=410)   | Asthma (n=500)  |                                   |          |
| Men                                               | 510 (56.0)                            | 340 (82.9)     | 170 (34.0)      | 32 (32.3)                         | 0.747    |
| Age, years                                        | 58.0 (16.3)                           | 67.8 (9.6)     | 49.9 (16.3)     | 47.8 (17.8)                       | 0.209    |
| Education level                                   |                                       |                |                 |                                   |          |
| No studies                                        | 71 (7.8)                              | 52 (12.7)      | 19 (3.8)        | 2 (2.0)                           | 0.224    |
| Primary education                                 | 416 (45.7)                            | 240 (58.5)     | 176 (35.2)      | 26 (26.3)                         |          |
| Secondary education                               | 249 (27.4)                            | 76 (18.5)      | 173 (34.6)      | 42 (42.4)                         |          |
| University degree                                 | 174 (19.1)                            | 42 (10.2)      | 132 (26.4)      | 29 (29.3)                         |          |
| Clinical data                                     |                                       |                |                 |                                   |          |
| Smoking history                                   |                                       |                |                 |                                   |          |
| Current smoker                                    | 128 (14.1)                            | 91 (22.2)      | 37 (7.4)        | 6 (6.1)                           | 0.016    |
| Ex-smoker                                         | 414 (45.5)                            | 305 (74.4)     | 109 (21.8)      | 35 (35.4)                         |          |
| Never smoker                                      | 368 (40.4)                            | 14 (3.4)       | 354 (70.8)      | 58 (58.6)                         |          |
| Duration of disease, years                        | 13.5 (10.6)                           | 10.5 (8.2)     | 16.0 (11.6)     | 17.9 (12.3)                       | 0.151    |
| Previous inhaler education                        | 690 (80.0)                            | 310 (80.5)     | 380 (79.5)      | 62 (63.9)                         | 0.001    |
| Asthma Control Test (ACT) $\geq 20$               | 289 (57.8)                            | NA             | 289 (57.8)      | 66 (66.7)                         | 0.257    |
| COPD assessment test (CAT) $\leq 10$              | 91 (22.2)                             | 91 (22.2)      | NA              | NA                                |          |
| Pulmonary function tests                          |                                       |                |                 |                                   |          |
| FEV <sub>1</sub> prior to bronchodilator test, mL | 2026 (982.8)                          | 1587 (924.1)   | 2,380.7 (881.3) | 2434.9 (981.3)                    | 0.718    |
| FEV <sub>1</sub> prior to bronchodilator test, %  | 68.5 (24.5)                           | 52.0 (18.3)    | 81.8 (20.5)     | 79.6 (20.6)                       | 0.432    |
| FEV <sub>1</sub> after bronchodilator test, mL    | 2123.4 (960.4)                        | 1571.4 (732.8) | 2574.5 (886.2)  | 2548 (919.4)                      | 0.832    |
| FEV <sub>1</sub> after bronchodilator test, %     | 74.0 (26.4)                           | 55.9 (20.1)    | 88.7 (21.3)     | 86.3 (19.4)                       | 0.211    |

\*Comparison between asthma patients in the self-reported and electronic adherence groups. Data as frequencies and percentages in parentheses unless otherwise stated.

#### Classification of adherence levels with the 10-items TAI

The sensitivity, specificity, and positive and negative predictive values of the 10-items TAI scores for identifying the groups of adherent, intermediate adherent and non-adherent patients are shown in Table 4. Cut-offs with the most favorable balance between sensitivity and specificity were 50 for adherent patients, 46 to 49 for intermediate adherent patients, and  $\leq 45$  for non-adherent patients. The ROC curves for the groups of adherent and non-adherent patients are shown

in Figure 2. The percentages of adherent patients were significantly higher in the electronic adherence group than in the self-reported adherence group (49.5% vs. 37.5%,  $p=0.02$ ) but the distribution of intermediate adherent patients was similar. The rates of non-adherence were also higher in the self-reported adherence group (Fig. 3). A good correlation ( $\rho=0.3$ ,  $p=0.01$ ) was found when adherence levels between self-reported and electronic adherence groups were compared.

#### Clinically guide of the non-adherence behavior patterns with the 12-items TAI

The 12-items TAI instrument allowed the classification of three non-adherence patterns. In both groups of self-reported and electronic adherence, erratic behavior was the most

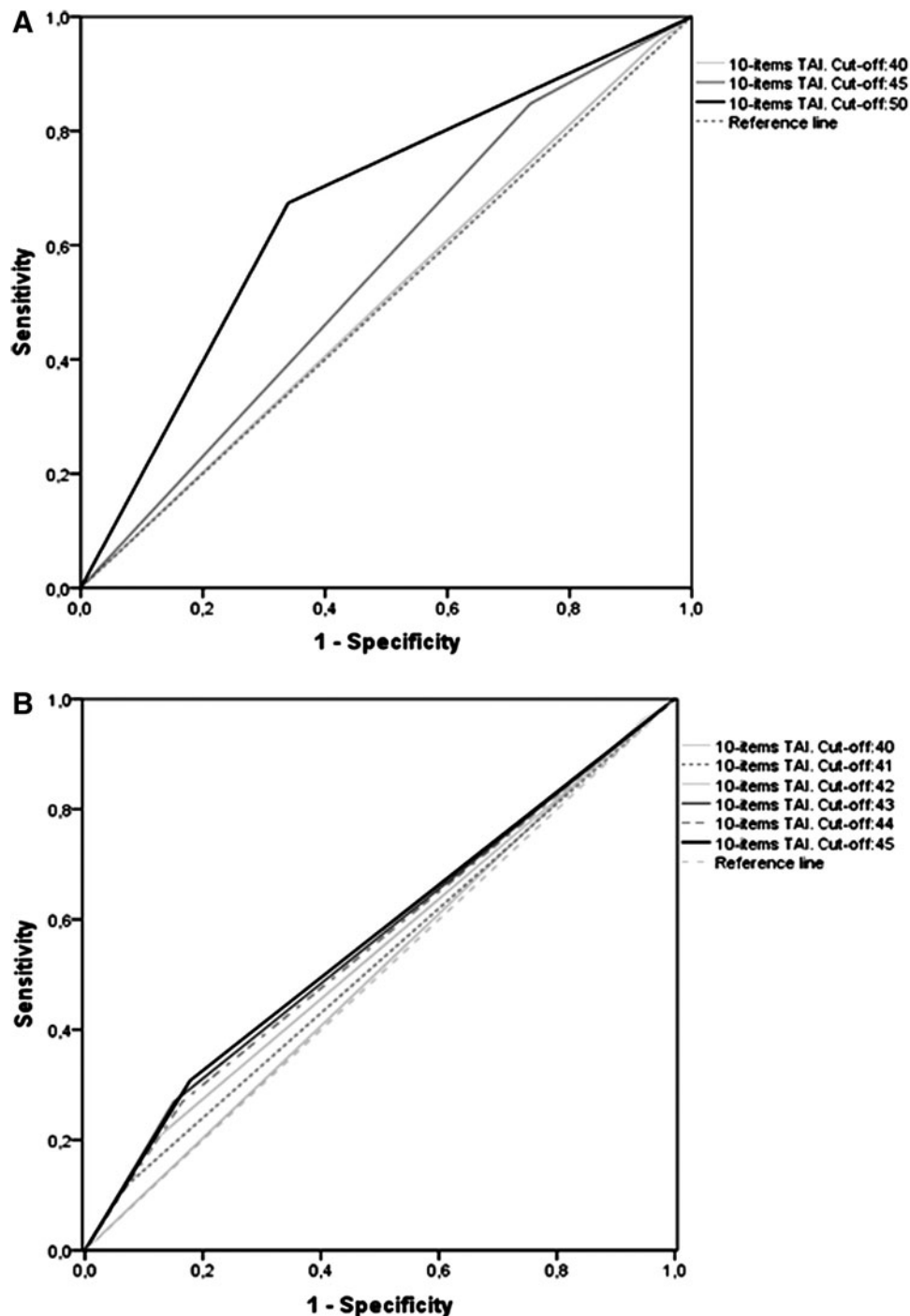
TABLE 3. TAI SCORES IN THE STUDY POPULATION

| Study groups                          | Patient domain score (items #1 to #10) | Health care professional domain score (items #11 and #12) |
|---------------------------------------|----------------------------------------|-----------------------------------------------------------|
| Self-reported adherence group (n=910) |                                        |                                                           |
| Mean (SD)                             | 46.1 (5.2)                             | 3.7 (0.6)                                                 |
| Median (minimum; maximum)             | 48 (18; 50)                            | 4 (2; 4)                                                  |
| Electronic adherence group (n=99)     |                                        |                                                           |
| Mean (SD)                             | 47.6 (3.7)                             | 3.8 (0.4)                                                 |
| Median (minimum; maximum)             | 49 (30; 50)                            | 4 (2; 4)                                                  |
| P value*                              | 0.005                                  | 0.084                                                     |

\*Comparison between self-reported and electronic adherence groups.

TABLE 4. SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES OF THE DIFFERENT CUT-OFFS OF THE 10-ITEMS TAI SCORE

| Cut-offs TAI scores* | Sensitivity (%) | Specificity (%) | Predictive value |              |
|----------------------|-----------------|-----------------|------------------|--------------|
|                      |                 |                 | Positive (%)     | Negative (%) |
| 50                   | 67.4            | 66.0            | 63.3             | 70.0         |
| 49                   | 78.3            | 50.9            | 58.1             | 73.0         |
| 48                   | 80.4            | 43.3            | 55.2             | 71.9         |
| 47                   | 84.8            | 30.2            | 51.3             | 69.6         |
| 46                   | 84.8            | 26.4            | 50.0             | 66.7         |
| 45                   | 84.8            | 22.6            | 48.8             | 63.2         |



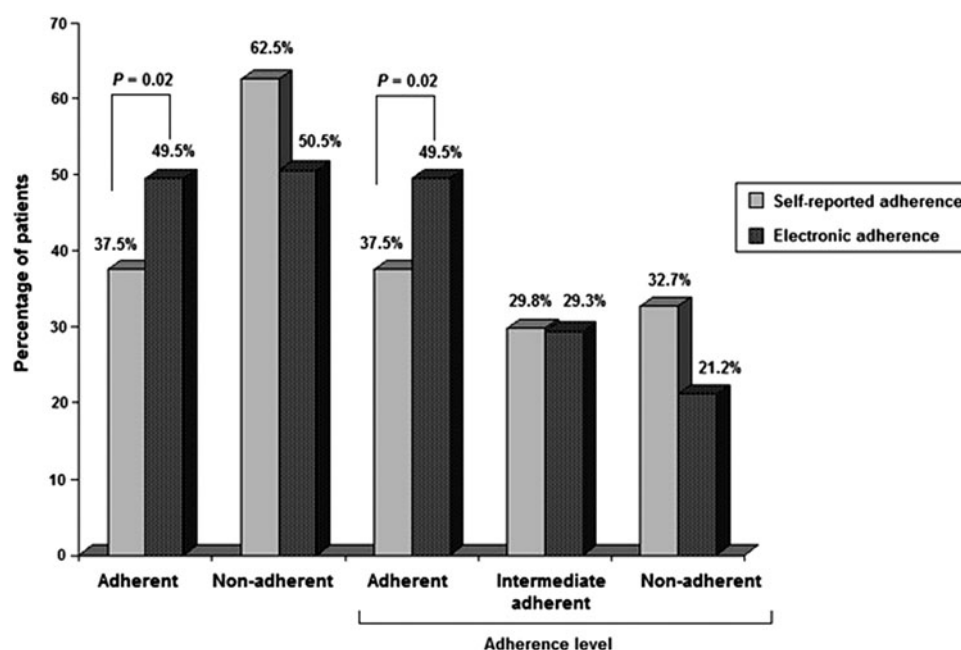
**FIG. 2.** ROC curves for the classification of adherent (AUC=0.7) and non-adherent (AUC=0.6) patients using a cut-off of the 10-items TAI questionnaire of 50 and  $\leq 45$ , respectively.

frequent, followed by deliberate and unwitting behaviors (Table 5).

#### *Comparison between TAI and the Morisky-Green test*

As compared to the Morisky-Green test, TAI showed a slightly better psychometric parameters, with a  $\rho=0.286$  for the correlation between 10-items TAI scores and Smart-inhalers records of the electronic group patients, and a

$\rho=0.247$  for the correlation between Smart-inhalers records of the electronic group patients and the Morisky-Green test scores. The kappa statistics was 0.33 for the 10-items of the TAI questionnaire and 0.28 for the Morisky-Green test. Regarding the ability to identify adherent and non-adherent patients, the 10-items TAI showed an intermediate position between the rates observed with the Smart-inhaler electronic devices and the Morisky-Green test (Table 6).



**FIG. 3.** Overall adherent and non-adherent percentages of patients and adherence levels in the self-reported ( $n=901$ ) and electronic ( $n=99$ ) adherence groups with the 10-items TAI.

## Discussion

This study shows the validity of a new questionnaire to assess adherence to inhaled medication in patients with asthma or COPD. The TAI instrument possesses good psychometric properties and has been shown not only to be adequate to classify asthma and COPD patients as adherent or non-adherent to inhaled therapy, but also to recognize the predominant pattern of non-adherence behavior in individual patients. Moreover, the questionnaire is short and easy to use for patients of different ages and education levels, providing a cheap, quick, and efficient way of obtaining information on inhaler adherence and non-adherence patterns, applicable to daily practice.

In the present study using a valid qualitative methodology, a total of 12 conditions or barriers to the use of inhalers, which have been related to the control of respiratory diseases in previous studies,<sup>(29–32)</sup> were formed by a consensus of a large group of health care professionals and thereupon, in a large sample of patients. Questionnaires available up to date<sup>(8–10,29)</sup> have also assessed some conditions included in the TAI, although in a partial way including forgetfulness,

lack of need of inhaler use, side effects-related concern and availability of the inhaler. However, none of these single barriers has shown predictive validity in the adherence to inhalers.

Since TAI in the extent that covers a wider range of situations (in comparison to its predecessors) and has been shown its viability in the health care setting, it may be a valuable tool for clinical use. Also, a novel aspect of the questionnaire is the inclusion of health care professionals' assessment of the patient's ability with the use of his/her inhaler. The patient competence in handling the device is a prerequisite for adherence. Therefore, based on the methodology used in the development of the TAI, the 12 conditions assessed by the instrument are clinically relevant to determine the level of adherence to inhalers.

The large study population of patients with COPD and asthma recruited by almost 200 specialists in different health care settings allowed a study of a representative sample of the patients with asthma and COPD, their treatment, and, therefore the main barriers modulating patient–physician

**TABLE 5.** NON-ADHERENCE BEHAVIOR PATTERNS ORIENTED WITH THE 12-ITEMS TAI

| Non-adherence pattern* | Self-reported adherence group ( $n=910$ ) | Electronic adherence group ( $n=99$ ) |
|------------------------|-------------------------------------------|---------------------------------------|
| Erratic                | 530 (58.2)                                | 48 (48.5)                             |
| Deliberate             | 376 (41.3)                                | 26 (26.3)                             |
| Unwitting              | 242 (26.6)                                | 19 (19.2)                             |

\*Frequency of non-adherent patterns is higher than 100% because more than one non-adherent pattern may be present in the same patient.

**TABLE 6.** ABILITY TO IDENTIFY ADHERENT AND NON-ADHERENT PATIENTS WITH SMART-INHALER DEVICE, 10-ITEMS TAI, AND MORISKY-GREEN TEST IN ELECTRONIC ADHERENCE GROUP

|                                | Smart-inhaler electronic device | 10-items TAI questionnaire | Morisky-Green test |
|--------------------------------|---------------------------------|----------------------------|--------------------|
| Adherent patients, $n$ (%)     | 46 (46.5)                       | 49 (49.5)                  | 52 (52.5)          |
| Non-adherent patients, $n$ (%) | 53 (53.5)                       | 50 (50.5)                  | 47 (47.5)          |
| Total patients                 | 99                              | 99                         | 99                 |

relationship, satisfaction, and health care system functioning that may affect adherence. Accordingly, the study sample was adequate to assess adherence to inhalers in both diseases from an overall perspective.

On the other hand, the inclusion of electronic devices provided reliable data on adherence in a group of participants. This objective measure of adherence, which is unusual in validation studies of other questionnaires probably because of the high cost, guaranteed robustness of the validation process. Scores of the 10-items and 12-items TAI were directly and positively correlated with data recorded with the Smart-inhalers, and differences between patients classified as adherents and non-adherents were also statistically significant. The observation that correlations, although statistically significant, were somewhat low may be explained by the fact that self-reported adherence is less reliable than electronic measures,<sup>(33)</sup> and the lower sample size in the electronic adherence group which probably prevented to achieve better correlation levels.

The differences in sociodemographic and clinical characteristics between patients in the electronic adherence group (higher percentage of women and education level) and the self-reported adherence group (combination of asthma and COPD patients, with a lower percentage of women and education level) do not question the validation of TAI. Results obtained in the electronic adherence group will be potentially generalizable to a similar population and also be subjected to similar adherence-related difficulties or barriers. It is possible that clinical and sociodemographic characteristics of the electronic adherence group may be the reason for significantly better TAI scores in this group as compared to the self-reported adherence group. Also, the large number of patients in the self-report adherence group versus the electronic adherence group probably determined that statistical significance could be easily reached. Despite these considerations, findings in the electronic adherence group provide solid evidence of the capacity of TAI to identify adherence to inhalers.

In relation to the electronic device monitoring, it should be noted that information recorded by the electronic devices not only includes whether the patient used the inhaler for a certain number of times, but also the hours at which the device was used during the "evaluation" days (in our study the 14 days between visits 1 and 2). This eliminates the possibility of dumping occurring immediately prior to the control visit because it would be registered that the patient used the inhaler on multiple occasions in that day and not in the expected mode (several times during the 14 days period). On the other hand, first readings of smart-inhalers on visit 1 were discarded to exclude the possible impact of the patient's training effect.

According to factor analysis of the two main components, different criteria for scoring these two dimensions were chosen. Clinical practice experience and the results of numerous studies<sup>34,35</sup> indicate that knowledge/recall of the prescription (item #11) and competence in using the inhaler (item #12) are prerequisites for adherence. Consequently, they play a differential role in adherence-related barriers, which logically also appeared statistically as a differential factor. This finding suggests that TAI may be used as a questionnaire of two measures with different applications: to identify adherence (10-items TAI, patient domain) and to have a clinical indication of the non-adherence behavior pattern (12-items TAI, both patient and health care professional domains).

The unidimensional structure of the 10-items TAI reflects the complexity of the adherence phenomenon. Studies in patients with respiratory disorders and other diseases<sup>36,37</sup> have shown that adherence is a particular complex issue, in which different barriers that compromise adherence have a low predictive capacity by themselves but combine and modify during the process of disease. In this respect, results of the present study show that when patients are classified by responses suggesting an erratic, deliberate, or unwitting non-adherence behavior pattern, the possibility to identify statistically different types of non-adherent patients was compromised.

This consideration, however, does not affect the internal validity of the instrument or the clinical usefulness of TAI. On the contrary, the percentages of non-adherence regarding the total number of items as well as grouped by the profile of non-adherence are sufficiently indicative of the importance of the problem and the value of the qualitative analysis of the items of each of the three non-adherence behaviour pattern. Accordingly, it is possible to identify quickly, reliably and objectively situations that may compromise adherence to inhaler devices that might otherwise go unnoticed in routine clinical practice.

There are some limitations of the study that deserves a comment. First, the lack of an electronic control group for COPD patients. Second, the weight of each adherence-related barrier according to different clinical and sociodemographic characteristics of patients with respiratory diseases and the inter-relationship among barriers were not assessed. Internal validity and clinical relevance of the study, however, are not affected by these limitations. In further studies, the Rash model approach as used by Kleppe et al.<sup>(38)</sup> in the development of a Probabilistic Medication Adherence Scale (ProMAS) tested in 370 elderly patients receiving medication for chronic conditions may be suggested to assess the construct validity of TAI.

In conclusion, TAI is a new questionnaire, specifically developed to identify non-adherence and specific adherence barriers involved in inhaled therapy. The study demonstrated the good psychometric properties of the questionnaire and validated their usefulness in the clinical setting. This could bring a new tool, to improve the patient's adherence to inhaler devices, according to their specific non-adherence pattern after implement tailored strategies.

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